

# Negative impact of laws regarding biosecurity and bioterrorism on real diseases

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## Abstract

Research on highly pathogenic microorganisms in biosafety level 3 and 4 laboratories is very important for human public health, as it provides opportunities for the development of vaccines and novel therapeutics as well as diagnostic methods to prevent epidemics. However, in recent years, after the anthrax and World Trade Center attacks in 2001 in the USA, the threat of bioterrorism has grown for both the public and the authorities. As a result, technical and physical containment measures and biosafety and biosecurity practices have been implemented in laboratories handling these dangerous pathogens. Working with selected biological agents and toxins is now highly regulated, owing to their potential to pose a threat to public health and safety, despite the fact that the anthrax attack was found to be the result of a lack of security at a US Army laboratory. Thus, these added regulations have been associated with a large amount of fruitless investment. Herein, we describe the limitations of research in these facilities, and the multiple consequences of the increased regulations. These limitations have seriously negatively impacted on the number of collaborations, the size of research projects, and, more generally, scientific research on microbial pathogens. Clearly, the actual number of known victims and fatalities caused by the intentional use of microorganisms has been negligible as compared with those caused by naturally acquired human infections.

**Keywords:** Biosafety, biosafety laboratory, biosecurity, bioterrorism, infectious disease, laws, limitations, regulations, select agent and toxins

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## Introduction

Research on highly pathogenic microorganisms in biosafety level 3 and 4 laboratories is critical for human public health, as it provides opportunities for the development of vaccines and novel therapeutics as well as improved diagnostic methods to prevent epidemics and optimize care for individual patients. However, working with these pathogens requires precautions that guarantee the safety of humans and the environment, as they may be disseminated because of a laboratory accident, poor laboratory practices, or intentional removal and subsequent release (bioterrorism attack).

According to the CDC, a bioterrorism attack constitutes the deliberate release of viruses or bacteria used to cause illness or death in people, animals, or plants. The first documented use of microorganisms as a bioweapon occurred in 1346 at Caffa (now Feodosia in Ukraine) by the Mongols, who catapulted the bodies of plague victims over the city walls to infect the surrounding population and encourage disease spread [1,2]. Since then, many microorganisms have been proposed as bioterrorism agents, and several attempts have been noted. In 1972, the Geneva Convention related to the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons, and their destruction, was ratified (<http://treaties.un.org/doc/Publication/UNTS/Volume%201015/volume-1015-I-14860-English.pdf>). However, many

signatory countries (including the Soviet Union and Iraq) continued research on and production of biological agents. For example, in 1979, it was found that the Russians had continued their studies on *Bacillus anthracis*, as revealed by an anthrax epidemic that resulted in 64 deaths in the city of Sverdlovsk (now Ekaterinburg). This incident occurred on a military facility, and resulted from an accidental release of anthrax spores [3]. Finally, a series of anthrax attacks occurred in the USA in 2001 [4,5], in which letters containing anthrax spores were mailed to several news media offices and two Democratic party senators, killing five people and infecting 17 others. Some observers were first tempted to link the attacks to al-Qaeda, although, on the basis of genomic analyses, investigators turned to an American microbiologist named Bruce Edwards Ivins. Dr Ivins was a principal investigator of a military laboratory at Fort Detrick (Maryland) that specialized in biological weapons; in particular, this laboratory contributed to the development of anthrax vaccines. Ivins had a history of mental health problems and was facing a difficult time professionally in 2001, because an anthrax vaccine that he was working on was failing [6]. It is of note that both of these accidents (in Russia and the USA) occurred at military institutes studying military biological weapons and/or microorganisms involved in bioterrorism. Subsequently, all countries working on these 'difficult' bacteria were penalized because of the mismanagement in these facilities. In particular, it has become increasingly difficult to work on plague and tularaemia, diseases that kill people naturally, unlike the 'bioterrorism attacks', which were actually caused by poor military management. Moreover, in recent years, the public has become increasingly concerned with the threat of bioterrorism. Indeed, the bioterrorism threat has been largely exaggerated by the media, fuelling unsubstantiated fear that is out of proportion to the actual threat. To illustrate this fact, according to the Information Web of Knowledge database, there are 6852 publications with the keyword 'bioterrorism' and 73 609 citations from 1995 to the present. During the same period, five people died following a false 'bioterrorism attack', which corresponds to a ratio of 1370 publications per death! For example, in France, no single case of bioterrorism has ever been identified. As previously described for some viral respiratory infections [7], the numbers of publications generated is disproportionate to the public health problem. By contrast, for example, tuberculosis kills c. 1.4 million people worldwide each year [8], and the emerging epidemic Beijing clone, which caused at least 13% of the tuberculosis deaths (180 000), led to 856 publications, giving a total of 1596 citations through 2013 [7] and a ratio of 0.0047 publications per death!

It goes without saying that the scientific community must alert the public of emerging infections and the risks associated

with infectious agents. However, the reactions must remain proportional to the number of cases and deaths, as this has a significant impact on governments and international agencies and the strategic decisions implemented.

Both the anthrax attacks and the World Trade Center attack in September 2001 have led to significant increases in US government funding for biological warfare research and preparedness.

More than 180 pathogens have been reported as potential agents for bioterrorism (Table 1). The CDC has classified these agents into three different categories according to their infectiousness, virulence, public perception, impact, and cost and sophistication of countermeasures [9]. Category A includes the most dangerous microorganisms that can be easily disseminated or transmitted from person to person, facultatively resulting in high mortality, with potential impacts in terms of public health. These pathogens may cause public panic and social disruption, and require specific actions for public health preparedness. Category B includes agents that are moderately easy to disseminate, cause moderate morbidity and low mortality, and require enhancement of diagnostic capacities and specific surveillance. Category C includes emerging infectious agents that could be engineered for mass dissemination in the future because of their availability and ease of production and dissemination, as well as their potential to cause high rates of morbidity and mortality and to have a major health impact. After 2001, a broader system of controls related to the possession, use and transfer of select agents was established, including imprisonment and fines. Biological select agents and toxins (BSATs) are defined by the US Department of Health and Human Services and the US Department of Agriculture in accordance with the CDC. These BSATs are considered to be pathogens or biological toxins that have the potential to pose a severe threat to public, animal or plant health, and are divided into three categories: (i) US Department of Health and Human Services select agents and toxins affecting humans; (ii) US Department of Agriculture select agents and toxins affecting agriculture; and (iii) overlap select agents and toxins affecting both ([http://www.selectagents.gov/resources/List\\_of\\_Select\\_Agents\\_and\\_Toxins\\_2013-09-10.pdf](http://www.selectagents.gov/resources/List_of_Select_Agents_and_Toxins_2013-09-10.pdf)).

The real fear of bioterrorism started after 2001, when hijacked aircraft were used as missiles, and the anthrax attacks followed in the wake of these events. These bioterrorism events, unlike others before them and irrespective of their actual very limited size, had a global impact and changed the perception of the public. Moreover, bioterrorism has been sensationalized by the media, and the perceived threat is now far greater than the real threat. Because we have not yet suffered a mass biological warfare event, the proposed bioterrorism scenarios can be challenged and, indeed, seem

**TABLE 1.** List of potential bioterrorism agents

Category	Bacteria	Viruses	Toxins	Parasites
A	<i>Bacillus anthracis</i> (anthrax) <i>Yersinia pestis</i> (plague) <i>Francisella tularensis</i> (tularemia) <i>Brucella</i> species (brucellosis) Food safety threats (e.g. <i>Salmonella</i> species, <i>Escherichia coli</i> O157:H7, <i>Shigella</i> , <i>Staphylococcus aureus</i> )	Variola virus (smallpox) Haemorrhagic fever viruses (Ebola, Marburg, Lassa and Machupo viruses)	<i>Clostridium botulinum</i> toxin	—
B	Glanders ( <i>Burkholderia mallei</i> ) Meliodosis ( <i>Burkholderia pseudomallei</i> ) Psittacosis ( <i>Chlamydia psittaci</i> ) Q-fever ( <i>Coxiella burnetii</i> ) Typhus ( <i>Rickettsia prowazekii</i> ) Cholera ( <i>Vibrio cholerae</i> ) Multidrug-resistant <i>Mycobacterium tuberculosis</i>	Viral encephalitis (alphaviruses, e.g. Venezuelan, eastern or western equine encephalitis)	Epsilon toxin of <i>Clostridium perfringens</i> Ricin toxin of <i>Ricinus communis</i> Abrin toxin of <i>Abrus precatorius</i> Staphylococcal enterotoxin B	<i>Cryptosporidium parvum</i>
C		Nipah virus Hantavirus SARS H1N1 HIV/AIDS Encephalomyelitis viruses (TBE, others)	—	—

HIV, human immunodeficiency virus; TBE, Tick Borne Encephalitis.

very unlikely. If such an event were to occur, the social impact could be catastrophic, as was the case in 2001 after the anthrax attacks in the USA; in France, for example, >4500 suspicious parcels were identified, but no toxic product was found [10].

In recent decades, authorities and researchers have developed regulations and guidelines that describe containment measures and working instructions, especially for select agents and toxins that are biological agents or biological toxins that have the potential to be used in acts of bioterrorism and pose a severe threat either to public health and safety or to agricultural plants and animals. Multiple, complementary and sometimes overlapping biosafety and biocontainment requirements exist worldwide, and sometimes these regulations are open to interpretation, and are consequently and logically subject to misinterpretation. All of these measures, in accordance with the increased importance of biosafety and biosecurity, as discussed above, have severe consequences for laboratories and even greater consequences for reference laboratories. In the great majority of cases, this especially concerns biosafety level 3 laboratories, as the number of level 4 laboratories in the world is relatively small.

## Literature Review

### Putative intentional use of pathogens involved in bioterrorism vs. natural hazards

In recent years, emerging and re-emerging infections, as well as the risk of bioterrorist events, have attracted increasing attention from health authorities, because of the epidemic potential that makes some of them a real public health challenge [11,12]. It is also interesting to draw a comparison

between natural cases of infection and the intentional use of microorganisms in bioterrorism. First, c. 15 million (>25%) of the 57 million annual deaths worldwide are estimated to be related directly to infectious diseases [13]. These data exclude the additional millions of deaths that occur as a consequence of infections or complications. Incidents involving biological weapons during the latter half of the 20th century were scarce. Moreover, it is challenging to describe the epidemiology of agents of bioterrorism, because some research has been conducted by military or state organizations, with only a small percentage of their activities being publically reported; hence, it can be difficult to distinguish between natural and intentional events. The Chemical and Biological Weapons Nonproliferation Project at the Monterey Institute Center compiled a list of the chemical, biological and nuclear attacks worldwide [14]. This analysis noted that, between 1960 and 1999, only eight criminal attacks with biological agents led to casualties, inflicting a total of 29 deaths and 31 injuries. As shown in Table 2, on comparison of the number of natural infections caused by dangerous bacteria (<http://www.cdc.gov/plague/maps/index.html>; [http://www.bt.cdc.gov/agent/smallpox/faq/smallpox\\_disease.asp](http://www.bt.cdc.gov/agent/smallpox/faq/smallpox_disease.asp); <http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf>; <http://www.who.int/csr/resources/publications/plague/whocdscsredc992a.pdf>; [15–19]; <http://www.cdc.gov/rmsf/stats/>) with infections caused by bioweapons [20], it is clear that the natural threat is much greater than the intentional threat. Indeed, casualties resulting from intentional attacks are insignificant as compared with the burden of morbidity and mortality associated with natural infectious diseases. In conclusion, it is essential to focus research and investigations on the natural emergence of deadly and contagious infectious disease rather than on putative bioterrorism attacks.

**TABLE 2. Comparison between the number of natural infections (per year) caused by some dangerous microorganisms and those caused by bioweapons in the last 40 years**

Type of disease and biological agent	No. of natural infections in humans each year	Percentage of deaths	References	Used as bioweapon the last 40 years; if yes, no. of injuries and deaths
Plague	c. 2000 cases	40–100% untreated	<a href="http://www.cdc.gov/plague/maps/index.html">http://www.cdc.gov/plague/maps/index.html</a> ;	No
Yersinia pestis	Estimated c. 2000 cases worldwide	8–10% treated	<a href="http://www.who.int/csr/resources/publications/plague/whocdscsredc992a.pdf">http://www.who.int/csr/resources/publications/plague/whocdscsredc992a.pdf</a>	Yes, 19 injuries and five deaths [20]
Anthrax	(sporadic cases in the majority)	20–100% untreated	( <a href="http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf">http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf</a> ) [15]	
Bacillus anthracis	EU and EEA countries c. 11 cases	1–50% treated		
Tularaemia	USA c. 125 cases	30% untreated	( <a href="http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf">http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf</a> ) [17]	No
Francisella tularensis	EU and EEA countries c. 900 cases	2% treated	( <a href="http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf">http://www.ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf</a> ) [18]	No
Brucellosis	500 000 cases (all Brucella species)	2–5% untreated		No
Brucella melitensis	EU and EEA countries c. 500 cases	Rarely fatal when treated		No
Typhus	Rare in the USA	10–40% untreated	[19]	No
Rickettsia prowazekii	Outbreaks in Africa and Russia	2–4% treated	( <a href="http://www.cdc.gov/rmsf/stats">http://www.cdc.gov/rmsf/stats</a> ) [16]	No
Rocky Mountain spotted fever	c. 2000 cases	20% untreated		No
Rickettsia rickettsii	USA, Central America, and South America	5–10% treated		No
Varicella	0 (last case in 1977)	30%	( <a href="http://www.bcr.cdc.gov/agent/smallpox/faq/smallpox_disease.asp">http://www.bcr.cdc.gov/agent/smallpox/faq/smallpox_disease.asp</a> )	No
Smallpox virus		But a vaccine exists		

EEA, European Economic Area.

### Costs of bioterrorism

Research on infectious agents, particularly BSATs, is vital for public health and national security. However, the long list of regulations and standards has an impact not only on the researchers but also on the administrative and support infrastructure of institutions engaging in research with infectious agents [21]. Scientists who choose to pursue the investigation of such pathogens will probably be confronted with a long and tortuous process.

Between 2001 and 2012, the federal government of the USA spent \$60 billion on biodefence efforts, according to analyses from the Center for Biosecurity of the University of Pittsburgh Medical Center in Baltimore, Maryland [22]. This money helped to modernize the public health system of the USA, and the BioShield project has prepared a stock of 20 million doses of the smallpox vaccine, 28.75 million doses of the anthrax vaccine, and 1.98 million doses of four drugs used to treat the complications of smallpox, anthrax, and botulism. However, as described by Hayden [22], much of the biodefence money did not go into research. For example, the CDC received most of the money (\$17.4 billion), and put the vast majority into public health infrastructure. In all, only \$11.99 billion of the \$60 billion was spent on programmes concerned with biodefence research (c. \$1 billion per year).

However, the increase in laws concerning BSATs and BSAT laboratories has had significant consequences, as the costs of ongoing security and safety largely exceed the funds received by institutions to cover the costs of facilities, maintenance, and operations. Thus, in the absence of continued funding, these institutions must be willing and able to commit funds to meet the additional financial burden. Dias *et al.* [23] conducted a bibliographic analysis of the *B. anthracis* and Ebola virus literature between 1992 and 2007 in the USA, to determine whether negative consequences of laws on BSATs could be detected. These authors noted that, after 2002, the number of publications concerning these two pathogens increased; however, the most striking effect observed was not associated with individual authors or institutions, and was instead associated with a loss of efficiency (increase of two-fold to five-fold in the cost of BSAT research).

In biosafety level 3 and 4 laboratories, limitations on research with regard to biosecurity regulations, safety considerations, research space limitations and physical constraints in experimental procedures are real. Furthermore, there will be several consequences of the reinforcement of regulations: (i) an increase in paperwork when transferring strains across the world, and strengthening of procedures for tracing strains; (ii) an increase in quality procedures for laboratories, particularly operations to maintain containment, worker protection, and

the protection of biological samples in the laboratories (e.g. people and sample movements, and waste and inactivation–sterilization protocols); (iii) modifications of biosafety level laboratories that are not yet compliant with the new regulations; and (iv) an increase in personnel training processes (longer and more complex training) [24,25]. All of these measures will have serious impacts on the budgets of laboratories, and will lead to a considerable loss of time, as well as inefficiency, in research and scientific publication.

More specific consequences associated with laboratory research areas have been noted since the establishment of new regulations (Table 3). The following section cites two examples.

This first example concerns our laboratory, 'URMITE'.

'Mediterranean Infection' is a university hospital institute that encompasses infectious diseases and tropical medicine at the University Hospital of Marseille, as well as diagnostic microbiology and parasitology, and serves as a national referral centre for the diagnosis of rickettsial diseases, and infections with *Coxiella* and *Bartonella* species, and *Francisella tularensis* (<http://www.mediterranean-infection.com>). Two main research units, URMITE and UMR190, currently produce >350 international scientific publications per year, and include 450 personnel (with 80 national and international students and PhD researchers). This laboratory coordinates European and international networks, serves as a leader in the research on several infectious diseases, including endocarditis, Whipple disease, rickettsial diseases, Q-fever, and arboviral disease, and is directly involved in defence against bioterrorism and highly contagious diseases.

Our laboratory is closely involved with the implementation of novel French regulations, particularly concerning BSATs. As a national reference centre for tularaemia and rickettsial diseases, which are considered to be caused by BSATs in France, our laboratory must follow and implement the regulations and specifications concerning biosafety level 3 laboratory structures. Since the implementation of the new law in 2013 in France [26], the research programmes concerning BSATs in our laboratory have been put on standby, while we await the decisions of the French national security agency. Moreover, there has been an increase in restrictive procedures (in handling, training, etc.) that have and will continue to have negative consequences for our laboratory in terms of efficiency, productivity, and development, as described above.

The second example concerns smallpox research.

Smallpox is believed to have emerged in the Middle East c. 6000–10 000 years ago, and this infection caused 500 million deaths in the 20th century alone [27,28]. Smallpox was largely erased as a result of the Jenner vaccine, and the last case of illness caused by this virus occurred in Somalia in 1977 [29]; the World Health Assembly (WHA) declared that smallpox had been officially eradicated in 1980. The last known stocks of variola virus are held by the USA at the CDC (consisting of 450 isolates) and in Russia at the State Research Centre of Virology and Biotechnology (approximately 150 samples, consisting of 120 strains) [30,31]. At the 60th Annual WHA in 2007, the WHO called for the destruction of known remaining stocks of the virus, to eliminate the risk of accidental release or theft, after multiple previous attempts. The final

**TABLE 3.** Examples of new requirements to be implemented in laboratories working on biological select agents and toxins (BSATs) in France following the publication of the decree of 26 June 2013 [26]

Types of requirement	Specifications and consequences
Personnel training	Each laboratory should establish an individualized training plan tailored to each activity. In fact, these training requirements, which also enable people to work on BSATs, exclude short-term trainees from participating in work on all or some BSATs. This could result in a heavy burden for some laboratories
Laboratories, equipment, and materials	The design and use of laboratories and equipment are based on the process of risk management, which involves many requirements in terms of resources; it is important to budget accurately before initiating work on BSATs. In addition, the validation, qualification, maintenance and monitoring of security and safety equipment will be a very important part of the operating expenses of the laboratory. The 'old' laboratories should expect compliance to result in significant expenditure
Management of subcontractor	The regulation precisely defines the role and responsibilities of each partner, and requires contracts for all operations relating to work on BSATs. The responsibility of the customer is clearly highlighted
Document management	Document management will help to ensure the traceability of all transactions and secure storage of documentation certifying implementation of biological safety and security measures. All of these documents must be available, which requires the implementation of a specific system of document management
Specific requirements for the use of vertebrate and invertebrate animals (arthropods) in work on BSATs	For animal experiments, these requirements impose constraints that were previously not mandatory. For example, vertebrate animals must have individual and permanent markings to ensure traceability of animals. For small laboratory rodents (mice and rats), the implementation of individual identification is complex, and significant additional costs are to be expected, depending on the technique used (tattoo, banding, microchip). For the handling of BSAT-infected arthropods, many additional precautions must also be taken. For example, regulations require systematic and rigorous counting of all individuals before and after manipulation, with all of the extra work that this imposes
Emergency plan and areas of restricted access	The laboratory will be required to set up an internal emergency plan for dealing with situations that may endanger its staff, the public, or the environment. It should also provide periodic simulation exercises. In developing this plan, the laboratory must work together with external services (prefecture, firefighters, police, etc.). Finally, security measures will also be needed to reduce the risk of BSATs being used for malicious purposes

deadline for a decision was postponed until 2011, because no consensus could be reached among the executive board of the WHO. The debate on whether or not the remaining stocks of smallpox virus should be destroyed is ongoing, and, in 2011, the WHA decided to postpone this debate until the 67th WHA in 2014, while limiting new research using the smallpox virus (allowing studies started before now to finish) [32–34].

However, we must keep in mind that the most serious concern related to smallpox is its conservation in laboratories. Indeed, the virus is ringfenced in the USA and Russia, although some stocks resulting from mass production of the virus include virulent forms and vaccination-resistant forms [35]. This is very worrying, as the two countries that possess stocks of smallpox virus are those in which the two anthrax releases occurred! Moreover, there are c. 50 genomes of human poxviruses and dozens of genomes of animal poxviruses available on the web (<http://www.poxvirus.org>). New institutional regulations forbid the sequencing of smallpox DNA longer than 500 bp, i.e. >20% of the total genome size, to avoid the reconstruction of the smallpox virus on the basis of its available genomes (<http://www.who.int/csr/disease/smallpox/SummaryrecommendationsMay08.pdf>, 2014). Because the USA and Russia possess stocks of smallpox virus, they may

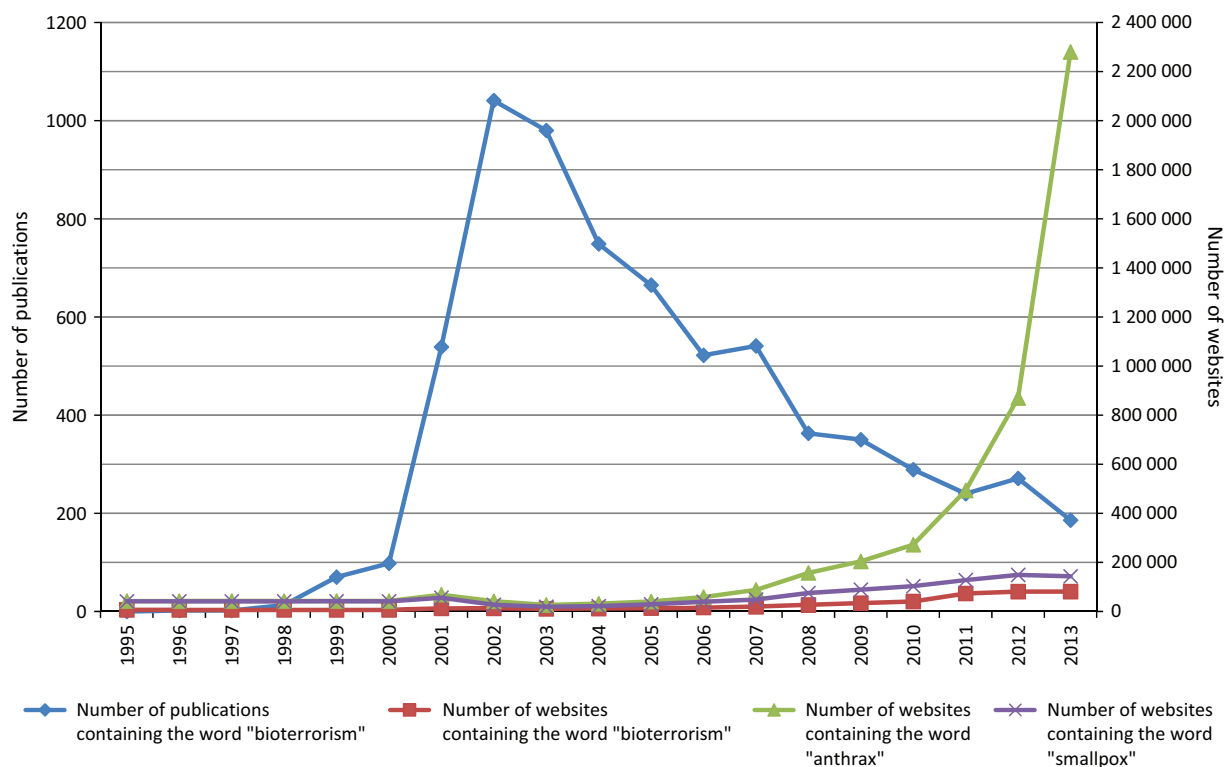
**TABLE 4.** Number of laboratories working on biological select agents and toxins and the number of authorization holders in France between 2011 and 2012 ([http://ansm.sante.fr/var/ansm\\_site/storage/original/application/4c74b962e250416cdb5c35dd8dfd46fb.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/4c74b962e250416cdb5c35dd8dfd46fb.pdf) page 124)

No.	2011	2012
Laboratories	266	122
Authorization holders	473	138

continue to quietly sequence smallpox strains, while other laboratories encounter difficulties concerning the identification and sequencing of new strains. For example, our laboratory was not authorized to sequence smallpox DNA from an ancient variola virus detected in a 300-year-old Siberian mummy [36].

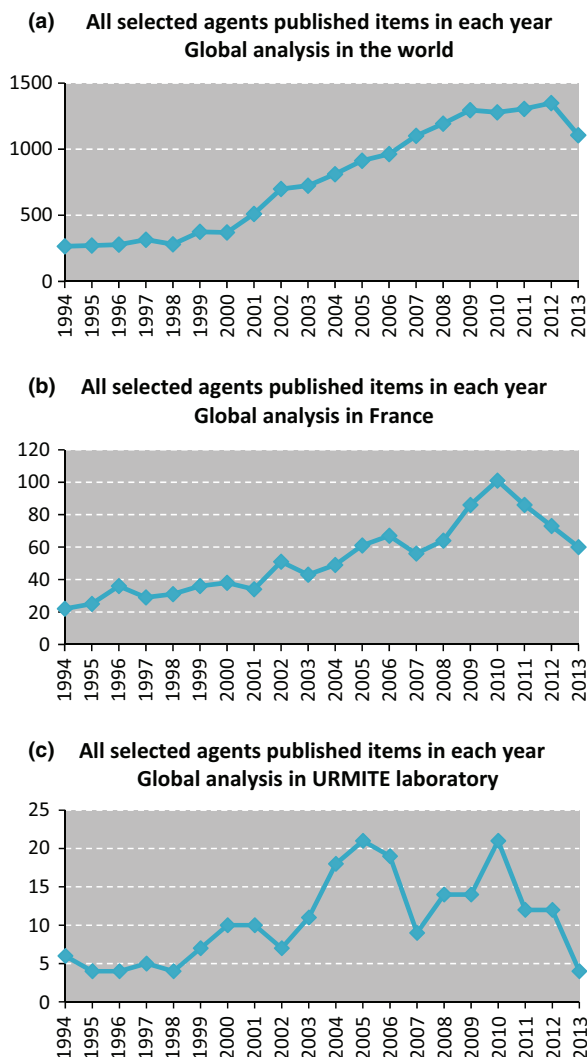
#### Effects on scientific production

Some laboratories have begun and will continue to withdraw from these research areas, which will produce a gap in the health network. In France, for example, as shown in Table 4 ([http://ansm.sante.fr/var/ansm\\_site/storage/original/application/4c74b962e250416cdb5c35dd8dfd46fb.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/4c74b962e250416cdb5c35dd8dfd46fb.pdf) page 124), the number of laboratories working on BSATs decreased by 54%, and the



**FIG. 1.** Published items collected from the Institute for Scientific Information Web of Knowledge (blue curve), and numbers of websites (found by a Google search) containing the words 'bioterrorism' (red curve), 'anthrax' (green curve) and 'smallpox' (purple curve) in the world between 1995 and 2013.





**FIG. 2.** Cumulative analysis of items published on bacterial biological select agents and toxins in each year. (a) Global analysis in the world. (b) Global analysis in France. (c) Global analysis in URMITE laboratory.

number of authorizations delivered decreased by 71%, between 2011 and 2012. A bibliometric analysis of the bioterrorism archival literature was conducted to determine whether negative consequences could be discerned, in which global research publications dealing with bioterrorism from 1995 to 2013 were retrieved from the Institute for Scientific Information Web of Knowledge (the term 'bioterrorism' was entered in the topic field). As shown in Fig. 1, this global analysis revealed that there was a publication peak following the 2001 attack, which decreased gradually in subsequent years.

A second global analysis was performed by searching the Institute for Scientific Information Web of Knowledge for the following bacterial BSATs: *Yersinia pestis*, *F. tularensis*, *Rickettsia*

*rickettsii*, *Rickettsia prowazekii*, *B. anthracis*, extensively drug-resistant *Mycobacterium tuberculosis*, and *Brucella melitensis* (the name of the bacterium involved was entered in the topic field). No time-span was selected, but the previous 20 years were displayed when possible. A citation report was created to represent a cumulative analysis of all bacterial BSATs cited for the above-mentioned items each year, both worldwide and in France and the URMITE laboratory (Fig. 2). Regarding the previous 'bioterrorism' search, a decrease in scientific publications was observed in 2013 as compared with other years. This reduction in publications was even more pronounced in France and the URMITE laboratory following the French implementation of two new laws addressing biosafety and biosecurity and BSATs (the first in 2010 and the second in 2013) [26,37].

This decrease in the number of scientific publications may have been the result of scientists redirecting their research to the study of attenuated strains that are not classified as BSATs or to other research areas. Simultaneously, collaborations between BSAT and non-BSAT laboratories may have been affected, especially overseas. Indeed, the development of diagnostics and vaccines may require the sharing of samples, recombinant DNA, or toxins, although research partners may be discouraged by the extensive and restrictive regulations. The consequence of these restrictions is the slowing down of research on organisms that pose a risk to humankind, irrespective of their potential to be utilized for bioweapon engineering.

## Conclusion

This review summarizes and documents the impacts of the increase in regulations concerning biosecurity, safety considerations, and research and personnel limitations for biosafety level 3 and 4 laboratories. Following the 11 September attacks in 2001, biosafety laboratories have evolved, and the regulations now demand higher stringency levels. Among many reports on biosafety, only a few have presented data regarding the evaluation and effectiveness of such restrictions; moreover, no criteria for judging their effectiveness have been reported. The BSAT regulations attempt to balance the need for regulating access to the most dangerous pathogens and minimizing regulatory burdens on basic biological research. However, if BSAT regulations are too tough, they may diminish long-term safety.

In recent years, the public has become increasingly concerned with the threat of bioterrorism. Indeed, the threat of bioterrorism has been greatly exaggerated by the media, and the perceived threat is now far greater than the actual threat.

Since the 11 September attacks, there has been an unparalleled demand for information on bioterrorism. For example, a Google search for web pages containing the word 'bioterrorism' yielded 6200 hits for 2000, 12 900 hits for 2001, and 8100 hits for 2013, regardless of any new, known bioterrorism events (Fig. 1). Moreover, the results were similar when the same search was performed with the term 'smallpox' or 'anthrax'. The handling of complex pathogens by isolated laboratory groups can hardly be considered in the context of bioterrorism; in this regard, most agents proposed to be potentially dangerous are not available technologically or cannot be used to create a significant impact. Rather, it is only at the state level that a number of pathogens could be militarized (as previously reported for Russia, for example). Apart from the anthrax cases observed in 2001, no successful example of the use of bacterial or viral agents has been observed. However, it has become very difficult to study plague and tularaemia—diseases that actually kill people—as a result of our erroneous, counterproductive response to the imagined or real threat of bioterrorism. In fact, the greatest success of bioterrorism activities could be seen as the clampdown on well-intended and important biomedical research. In this respect, the social consequences of bioterrorism in the field of science (with tangible repercussions for public health) have been spectacular.

We must therefore keep in mind that safety cannot be expressed in absolute terms, but rather represents a relative concept of tolerability and the limits of acceptability. Workers and regulators must try to find a balance between the costs of safety measures and the potential benefits for society and human health. Specialized governmental and institutional support is critical for researchers engaged in such highly regulated programmes for the discovery of new antivirals, therapeutics, vaccines and diagnostics for both bio defence and emerging pathogens.

## Transparency Declaration

No conflicts of interest declared.

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